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CONDENSED ISOQUINOLINES. 18*. ENAMINE PROPERTIES OF BENZ-IMIDAZO[1,2-*b*]ISOQUINOLIN-11(5H)-ONE IN THE MICHAEL REACTION

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The reaction of benzimidazo[1,2-b]isoquinolin-11(5H)-one with activated olefins has been studied. The derivatives of 3,10-dioxo-3H,10H-benzimidazo[1,2,3-ij]benzo[c][1,8]naphthyridine formed are the result of an initial Michael reaction at $C_{(6)}$ followed by intramolecular heterocyclization.

Keywords: heterocyclic enamines, derivatives of the 3,10-dioxo-3H,10H-benzimidazo[1,2,3-*ij*]benzo-[*c*][1,8]naphthyridine system, the Michael reaction.

The study of the properties and chemical reactions of enamines is one of the most actively developing regions of organic chemistry. Among the factors provoking the interest of chemists in this area the possibility of heterocyclization based on enamines occupies a special place [2-4], but the conjugated addition of activated olefins to heterocyclic enamines (the Michael reaction) as a method of heterocyclization has not been studied enough [5,6]. We have previously [1] studied the acylation and alkylation of benzamidazo[1,2-*b*]isoquinolin-11(5H)-one (**1**) with alkyl halides and have shown that attack occurs at the enamine fragment of the structure with formation of products in positions 5 and 6 depending on the nature of the reagent and the reaction conditions. In the present study it is shown that the enamine fragment of the tetracycle **1** undergoes conjugated addition with activated olefins to construct a pyridine ring in the system and suggest a suitable one-step method for the synthesis of previously inaccessible 1-aryl-substituted derivatives of benzimidazo[1,2,3-*ij*]benzo[*c*]-[1,8]naphthyridine from benzimidazo[1,2-*b*]isoquinolin-11(5H)-one **1**. The first examples of benzimidazo-[1,2,3-*ij*]benzo[*c*][1,8]naphthyridines were obtained [7] by condensation of 6-formylbenzimidazo[1,2-*b*]-isoquinolin-11(5H)-one with active methylene esters and acids.

On boiling compound **1** in 2-propanol in the presence of Et_3N with nitriles or esters of cyanocinnamic acid compounds **4a-c** and **7a-c** (method A) were obtained. They are products of consecutive reactions: conjugative Michael addition (attack at atom $C_{(6)}$ *via* intermediates of type **2** and **5**) with subsequent intramolecular acylation in the intermediate at atom $N_{(5)}$ (compounds of type **3** ⇄ **4** and **6**) (Scheme 1).

In the case of cyanocinnamate esters, the reaction did not stop at this point but proceeded further on oxidation of the intermediate **6** to **7**.

* For Communication 17 see [1].

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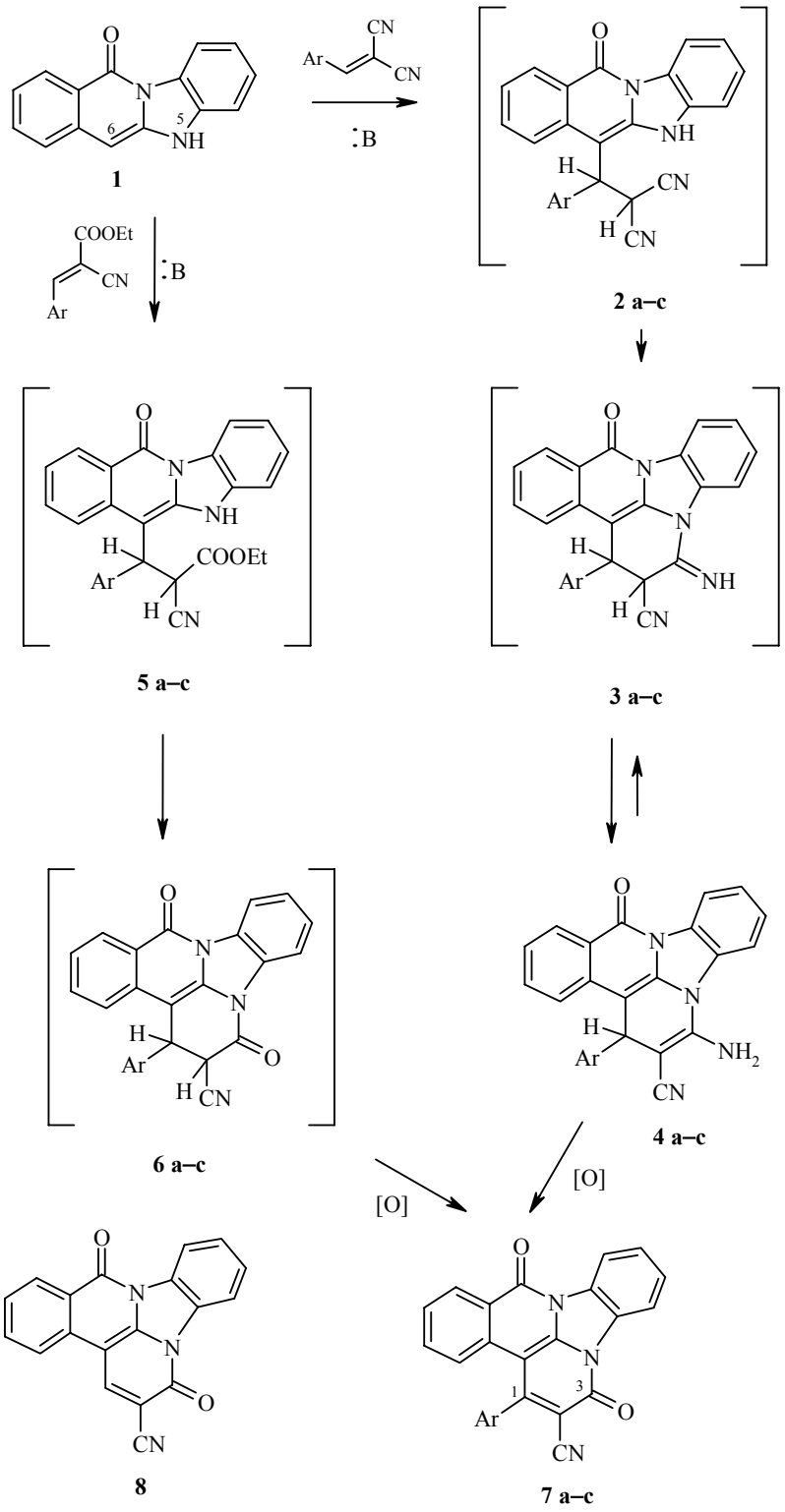

a Ar = 4'-ClC_6H_4; **b** Ar = 4'-$MeOC_6H_4$; **c** Ar = 4'-$Me_2NC_6H_4$

TABLE 1. Spectroscopic Characteristics of Compounds **4a-c**

Compound	IR spectra, ν, cm^{-1}			^{1}H NMR spectra (DMSO-d_6), δ, ppm (*J*, Hz)										
	Signals of the protons of the benzimidazo[1,2,3-*ij*]benzo[*c*][1,8]naphthyridine nucleus											Signals of substituents		
	C=O	CN	Other signals	H-8, d, *J* = 8.0	H-11, d, *J* = 8.0	H-5, d, *J* = 8.0	H-13, t, *J* = 8.0	H-6, t, *J* = 8.0	H-14, d, *J* = 8.0	H-7, t, *J* = 8.0	H-12, t, *J* = 8.0	H-1, s	NH_2, s	Ar
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
4a	1698	2180	3440, 3300 ($^{s,as}NH_2$)	8.60	8.32	7.94	7.59	7.47	7.41-7.38 (4H, m, H-7, H-14, H-3', H-5')		7.35	5.33	6.49	H-3', H-5'* 7.30 (2H, d, *J* = 8.0, H-2', H-6')
4b	1695	2180	3440, 3300 ($^{s,as}NH_2$), 1025 (C–O–C)	8.63	8.34	7.93	7.54	7.42	7.38–7.30 (3H, m)			5.17	6.24	7.20 (2H, d, *J* = 8.0, H-2', H-6'), 6.76 (2H, d, *J* = 8.0, H-3', H-5'), 3.70 (3H, s, $OC\underline{H}_3$)
4c	1695	2180	3440, 3300 ($^{s,as}NH_2$)	8.62	8.33	7.94	7.59	7.47 (2H, m)	7.39		7.35	5.15	6.35	7.14 (2H, d, *J* = 8.0, H-2', H-6'), 6.58 (2H, d, *J* = 8.0, H-3', H-5'), 2.80 (6H, s, $N(C\underline{H}_3)_2$)

* Superposition of signals of the benzimidazo[1,2,3-*ij*]benzo[*c*][1,8]naphthyridine nucleus and the signals of substituents, see columns 10 and 11.

TABLE 2. Spectroscopic Characteristics of Compounds **7a-c** and **8**

Compound	IR spectra, ν, cm^{-1}			^{1}H NMR spectra (DMSO-d_6), δ, ppm (*J*, Hz)									
				Signals of the protons of the benzimidazo[1,2,3-*ij*]benzo[*c*][1,8]naphthyridine nucleus									Signals of substituents, Ar
	C=O	CN	Other signals	H-5, d, *J* = 8.0	H-8, d, *J* = 8.0	H-11, d, *J* = 8.0	H-7, t, *J* = 8.0	H-6, t, *J* = 8.0	H-13, t, *J* = 8.0	H-12, t, *J* = 8.0	H-14, d, *J* = 8.0	H-1, s	
1	2	3	4	5	6	7	8	9	10	11	12	13	14
7a	1697 1663	2227		8.79	8.75	8.52	7.84-7.76 (2H, m)		7.58-7.49 (4H, m, H-12, H-13, H-3', H-5')		6.86		7.73 (2H, d, *J* = 8.0, H-2', H-6'), H-3', H-5'*
7b	1700 1659	2220	1035 (C–O–C)	8.79	8.75	8.51	7.83-7.75 (2H, m)		7.54	7.48	6.92		7.39 (2H, d, *J* = 8.0, H-2', H-6'), 7.21 (2H, d, *J* = 8.0, H-3', H-5'), 3.95 (3H, s, OC<u>H</u>$_3$)
7c	1694 1659	2222		8.77	8.74	8.50	7.81-7.74 (2H, m)		7.53	7.48	7.10		7.26 (2H, d, *J* = 8.0, H-2', H-6'), 6.91 (2H, d, *J* = 8.0, H-3', H-5'), 3.30 (6H, s, N(C<u>H</u>$_3$)$_2$)
8	1700 1668	2232		8.72	8.68	8.47 (2H, H-11, H-14)	7.80-7.72 (2H, m)		7.66	7.94	—*[2]	9.39	

* Superposition of signals of the benzimidazo[1,2,3-*ij*]benzo[*c*][1,8]naphthyridine nucleus and the signals of substituents, see columns 10 and 11.

*[2] Superposition of signals of the benzimidazo[1,2,3-*ij*]benzo[*c*][1,8]naphthyridine nucleus, see column 7.

Taking into account studies on the acylation and alkylation of benzimidazoisoquinoline **1** [1,2], we did not exclude the possibility of addition of the olefin at position $N_{(5)}$. As evidence of the structures of 3-amino-1-aryl-10-oxo-1H,10H-benzimidazo[1,2,3-*ij*]benzo[*c*][1,8]naphthyridin-2-carbonitriles (**4a-c**) and 1-aryl-3,10-dioxo-3H,10H-benzimidazo[1,2,3-*ij*]benzo[*c*][1,8]naphthyridin-2-carbonitriles (**7a-c**) we used the model compound 3,10-dioxo-3H,10H-benzimidazo[1,2,3-*ij*]benzo[*c*][1,8]naphthyridin-2-carbonitrile (**8**) [7]. We observed a great degree of similarity of the absorptions in the IR spectra of the carbonitrile **8** and compounds **7a-c**. The presence of absorption bands of two carbonyl groups (1700, 1660 cm^{-1}) and $\nu_{(CN)}$ bands of medium intensity (222-2237 cm^{-1}) were characteristic The signal of the $C_{(1)}H$ proton (in the region of 9.3 ppm), characteristic for structure **8** was absent from the ^1H NMR spectra of compounds **7a-c**, while the signals of the aromatic protons $C_{(12)}\underline{H}$ and $C_{(14)}\underline{H}$ in compounds **7a-c** were observed at stronger fields (7.48 and 6.90 ppm respectively, see Table 2) than in compound **8** (7.94 and 8.47). The latter fact is fully explained by the electronic effect of the aryl substituent at $C_{(1)}$ on $C_{(12)}\underline{H}$ and the additional effect of the magnetic anisotropy of the 1-aryl substituent on the resonance of $C_{(14)}\underline{H}$.

In the ^1H NMR spectra of compounds **4a-c** the amino groups appear in the range 6.2-6.4 ppm as broad two proton signals and in the IR spectra as two bands, $\nu^{s}_{NH_2}$ (3440 cm^{-1}) and $\nu^{as}_{NH_2}$ (3300 cm^{-1}). A single band was observed in the carbonyl stretching region (1695 cm^{-1}), while there is a low frequency shift of the nitrile vibration (2180 cm^{-1}) relative to those for **7a-c**, in agreement with lower electron acceptor properties of the substituents at $C_{(3)}$. We assign a one proton singlet in the region of 5.1-5.3 ppm region in the ^1H NMR spectra of **4a-c** to the proton $C_{(1)}\underline{H}$. According to the spectroscopic data, the iminoform tautomer **3** is absent.

The 3,10-dioxo derivatives **7a-c** were obtained in good yield (50-60%) on prolonged boiling of the 3-amino derivatives **4a-c** in acetic acid, which indicates the link between systems obtained and with the structure **8**.

EXPERIMENTAL

Melting points of the compounds synthesized were measured on a Boetius block and were not corrected. IR spectra of KBr tablets were recorded with a Pye-Unicam SP3-300 instrument. ^1H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were measured on a Mercury 400 (Varian) (400 MHz) instrument. Assignments of the signals of the aromatic protons were confirmed by COSY HH spectra for compounds **4c** and **8**. The progress of reactions and the purity of the compounds prepared were monitored by TLC on Silufol UV-254 strips.

5,11-Dihydrobenzimidazo[1,2-*b*]isoquinoline-11-one **1** was prepared according to [8], 2-arylidene-malonitriles and ethyl 3-aryl-2-cyano-2-propenoates according to [9], and 3,10-dioxo-3H,10H-benzimidazo[1,2,3-*ij*]benzo[*c*][1,8]naphthyridin-2-carbonitrile **8** according to [7]. Their constants corresponded to those recorded.

3-Amino-1-aryl-10-oxo-1H,10H-benzimidazo[1,2,3-*ij*]benzo[*c*][1,8]naphthyridin-2-carbonitriles (4a-c). A mixture of benzimidazoisoquinoline **1** (2.34 g, 10 mmol), 2-arylidenemalonitrile (15 mmol), and Et_3N (2 ml) in 2-propanol (20 ml) was refluxed for 6 h. The mixture was cooled, the yellow precipitate was filtered and carefully washed with ethanol. It was recrystallized from DMF.

Compound 4a.Yield 3.08 g (73%); mp 335-337°C (DMF). Found, %: C 70.93; H 3.60; Cl 8.30; N 13.26. $C_{25}H_{15}ClN_4O$. Calculated, %: C 71.01; H 3.58; Cl 8.38; N 13.25.

Compound 4b. Yield 3.09 g (74%); mp 283-285°C (DMF). Found, %: C 74.60; H 4.28; N 13.41. $C_{26}H_{18}N_4O_2$. Calculated, %: C 74.63; H 4.34; N 13.39.

Compound 4c. Yield 2.50 g (58%); mp 270-272°C (DMF). Found, %: C 75.06; H 4.83; N 16.29. $C_{27}H_{21}N_5O$. Calculated, %: C 75.16; H 4.91; N 16.23.

1-Aryl-3,10-dioxo-3H,10H-benzimidazo[1,2,3-*ij*]benzo[*c*][1,8]naphthyridin-2-carbonitriles (7a-c) (General Method A). A mixture of benzimidazoisoquinoline **1** (2.34 g, 10 mmol), ethyl 3-aryl-2-cyano-2-propenoate (15 mmol), and Et_3N (2 ml) in 2-propanol (20 ml) was refluxed for 3 h and then cooled. The yellowish precipitate was filtered off, washed carefully with ethanol, and recrystallized from DMF.

Compound 7a. Yield 2.15 g (51%); mp >340°C (DMF). Found, % C 71.10; H 2.77; Cl 8.32; N 10.00. $C_{25}H_{12}ClN_3O_2$. Calculated, %: C 71.18; H 2.87; Cl 8.40; N 9.96.

Compound 7b. Yield 2.21 g (53%); mp 326-328°C (DMF). Found, %: 74.72; H 3.59; N 10.10. $C_{26}H_{15}N_3O_3$. Calculated, %: C 74.81; H 3.62; N 10.07.

Compound 7c. Yield 2.02 g (47%); mp 325-326°C (DMF). Found, %: C 75.35; H 4.11; N 13.03. $C_{27}H_{18}N_4O_2$. Calculated, %: C 75.34; H 4.21; N 13.02.

Method B. A suspension of 3-amino-1-(4-dimethylaminophenyl)naphthyridine **4c** (4.31 g, 10 mmol) in acetic acid (25 ml) was refluxed for 10 h, cooled, the precipitate was filtered off, washed with acetic acid and ethanol, and recrystallized from DMF to give 1-(4-dimethylaminophenyl)-3,10-dioxonaphthyridine **7c**.

The 3,10-dioxonaphthyridines **7a,b** were prepared analogously.

Compound 7a. Yield 2.44 g (58%).

Compound 7b. Yield 2.09 g (50%).

Compound 7c. Yield 2.37 g (55%).

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